I

CHEMOTHERAPY: NEW REMEDIES IN THE TREATMENT OF SYPHILIS

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INTRODUCTION

MR. PRESIDENT, LADIES AND GENTLEMEN, I am deeply sensible of the honour you have done me in asking me to read a paper before you this evening, for, while chemotherapy has, on the whole, been somewhat neglected in this country, no such charge of neglect can be brought against this Society. The history of chemotherapy as a science, though comparatively short is, in one sense, unique, for while most sciences owe a debt to the work of many generations, the present status of chemotherapy is due almost entirely to the genius of one man, Paul Ehrlich. Ehrlich it was who first laid down the fundamental conceptions by means of which the progress of chemotherapy is destined to be guided for many years to come. Among these conceptions none is of greater importance than that of the chemotherapeutic index, defined as the relation between the toxicity of a compound for the body (organotropism) and toxicity for the parasite (parasitotropism), in other words, the relation between the maximum tolerated dose and the minimum curative dose. The aim of all chemotherapeutic research is to obtain compounds of ever greater toxicity to the parasite and ever smaller toxicity to the host, to attain eventually to the *therapia magna sterilisans*. In certain diseases, notably some helminthic infections and in kala azar a very close approximation to such a sterilising therapy has already been reached, but in syphilis, despite the advances that have been made in the last quarter of a century much work is still needed before it can be truthfully said that the spirochæte of syphilis has been eradicated from the tissues. There is in fact a danger that to-day with the rapid cure of clinical symptoms produced by many anti-syphilitic drugs we may be further away from such a complete sterilisation of the tissues than we

were when prolonged treatment with mercury presented the only available means of therapy.

There is therefore still ample incentive to discover and perfect new anti-syphilitic drugs, and that the search for such remedies is by no means slackening will be my endeavour to demonstrate this evening. Before describing certain of these newer compounds it is perhaps not out of place to discuss very briefly the use of experimental animals in the search for anti-syphilitic drugs. It would be as unjustifiable as it would be impossible to test every new remedy of unknown toxicity on man, and therefore the use of some experimental animal is essential. If that animal is at the same time suffering from an infectious condition it is possible to obtain a chemotherapeutic index and thus to compare directly the parasitocidal activity of the new compound with that of older remedies. The progress of chemotherapy is thus bound up not only with the increasing skill of the research chemist but with the advances made by the experimental pathologist in reproducing in laboratory animals the diseases to which man is heir. It was, for instance, only after Laveran and Mesnil (1902) had found that trypanosomiasis could be produced experimentally in mice and rats that it was possible for Ehrlich and Shiga (1904) to undertake therapeutic investigations in this field and to discover the trypanocidal dye, designated trypan red. Trypanosome infections in mice and rats are still used to a certain extent in the determination of spirochæticidal activity. The advantages of this type of infection are that the dose of the infecting organisms can be easily standardised and results are rapidly obtained. Unfortunately a parallelism between trypanocidal and spirochæticidal action is limited to very few of the trivalent arsenicals, arsphenamine, and to a lesser degree neoarsphenamine. Pentavalent arsenicals such as tryparsamide are highly trypanocidal but not spirochæticidal, while bismuth compounds are spirochæticidal but not trypanocidal.

Spirochætal infection in fowls due to *S. gallinarum* and relapsing fever in rodents have also been used for the evaluation of anti-syphilitic drugs. Apart from the fact that these diseases do not in any way resemble syphilis in man it is difficult to obtain standardised infections with the spirochætes of relapsing fever. The same objection applies to leptospiral jaundice in the guinea-pig, a disease, which

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though uninfluenced by arsenicals is susceptible to bismuth, for on passage, leptospira are liable to lose their virulence. More recently Frazer (1930) has proposed the use of *Spirillum minus* infections in rodents. Sodoku or rat-bite fever, especially in the rat, bears a certain resemblance to syphilis in man, but is affected only by arsenic compounds. Gold and bismuth, as was pointed out by Browning and his colleagues (1927), being without action in this disease.

At the present time the most suitable experimental conditions for the study of anti-syphilitic drugs are those presented by spontaneous spirochætal infection of the rabbit due to *S. cuniculi* and by true syphilis in the rabbit, despite certain disadvantages such as the length of time necessary for the lesion to develop. Experimental rabbit syphilis has now been extensively studied, more particularly at the Rockefeller Institute in New York, and its similarities and dissimilarities to human syphilis have been thoroughly canvassed. It must be admitted that the fact that a compound shows anti-syphilitic activity in rabbit syphilis does not necessarily prove that the same compound will be active in human syphilis. Thus Flumerin, the disodium salt of hydroxy mercuric fluorescein, which was introduced by White, Hill, Moore and Young (1922), was found to be rapidly curative in experimental syphilis of the rabbit but almost inactive in human syphilis. It may, however, be definitely stated that if a particular compound is without action in rabbit syphilis, it is extremely improbable that it will have any curative action in human syphilis. Provided then, that a compound gives a satisfactory chemotherapeutic index in the rabbit and that a sufficient number of animals have been employed to render the results statistically valid, a *primâ facie* case has been made out for a trial of the compound in human syphilis.

Some forty-five elements have now been investigated in regard to their action in experimental syphilis, trypanosomiasis and spirochætosis, of which, ten, namely, vanadium, arsenic, antimony, tellurium, platinum, gold, mercury, bismuth, gallium and indium have a definite spirochætotoxic action, while thorium also was found to be active by Klauder (1924), although Levaditi and Lépine (1931) regard it as inactive. The position of these elements in the periodic system of Mendeleeff

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does not reveal any striking similarity though Levaditi and Lépine (1931) suggest that all the elements with a curative action are similar electrochemically in being weakly electro-positive or weakly electro-negative. Their polarisation tension is below that of hydrogen, they do not decompose water at ordinary temperatures and they are all, with the exception of gallium, precipitated as sulphides by sulphuretted hydrogen. Otherwise, physically and chemically they appear to have nothing in common.

TRIVALENT COMPOUNDS

Arsenic.—While arsenic is employed in the treatment of syphilis both in the trivalent and pentavalent form, little fresh work has been done in the production of new trivalent compounds. The compound, introduced by Albert (1924) under the name of "Albert 102," though of considerable interest from the chemical point of view, in that it showed that neither the nuclear amino-group nor the nuclear hydroxy-group are absolutely essential to the development of therapeutic activity in the arsphenamine type of molecule, gave disappointing results both in syphilis and trypanosomiasis and has had no successors.

In 1915, Ehrlich and Karrer published details of complex salts of arsenobenzene and the heavy metals characterised by deep colours and great stability. Only silver arsphenamine and silver neoarsphenamine have found a place therapeutically, though Raiziss has introduced a bismuth arsphenamine compound under the name of bismarsen.

Recently also there has again been an attempt to show that arsphenamine can be prepared without the use of methyl alcohol which was originally employed by Ehrlich as a solvent for isolating the dihydrochloride of the arsphenamine base. Larsen (1931), on somewhat slender grounds, believes that the toxicity of arsphenamine is almost entirely due to the presence of methyl alcohol and its derivatives in the molecule, and that these can be eliminated if the arsphenamine is finally precipitated with a cold aqueous solution of hydrochloric acid. Some years ago Fargher and Pyman (1920) threw grave doubts on the feasibility of this method for the production of arsphenamine on a large scale.

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PENTAVALENT COMPOUNDS

Of the pentavalent arsenicals now in use, that of most importance is undoubtedly *Tryparsamide*, Sodium-*n*-phenylglycineamide-*p*-arsinate, originally prepared by Jacobs and Heidelberger (1919). It is a colourless crystalline salt, soluble in water and forming neutral solutions of considerable stability. It contains 24.57 per cent. of arsenic and is generally administered intravenously, although if it does infiltrate the tissues it does not produce necrosis but causes only a burning sensation similar to that experienced with sulpharsphenamine. Some workers, in fact, give it intramuscularly. In their original experiments Brown and Pearce (1919) found that, though in rabbit syphilis tryparsamide caused rapid healing of the primary lesions, yet it did not necessarily cause destruction of the spirochætes. Little interest was therefore taken in the compound for some years until after its beneficial effects in the nervous stages of sleeping sickness had been discovered, when an attempt was made to determine whether its action was similar in neurosyphilis, Voegtlin, Smith, Dyer and Thompson (1923) having found that tryparsamide possesses a higher penetrability for the central nervous system than arsphenamine and neoarsphenamine. As a result of the observations of Lorenz, Loevenhart, Bleckwenn and Hodges (1923), it was found that both clinical and serological improvement occurred in general paralysis after the administration of tryparsamide. These results were later confirmed by Lees (1925) in this country and by numerous other observers, more particularly in the United States of America, for on the Continent the use of tryparsamide has been almost entirely neglected. Sufficient time has now elapsed for a fairly correct evaluation of this compound in the treatment of general paralysis and tabes dorsalis. Unsatisfactory results obtained by Fordyce and Myers (1925) and Hecht (1927) were for the most part due to the administration of insufficient amounts of the drug. Schoch (1931) now recommends that at least 50 injections of never less than 1 gm. and preferably 3 gm. should be given at weekly intervals before all hope of improvement is finally abandoned. The type of neurosyphilis in which the greatest response to tryparsamide is to be expected is that in which the

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neurologic signs of degeneration in the cord are not well marked, while in general paralysis, cases of the expansive type apparently show the most improvement. The serological changes are thus summarised by Schoch (1931):—

Blood Wassermann reaction reversed in 41 per cent.,
reduced in 12 per cent.

Spinal fluid Wassermann reaction reversed in 27 per cent., reduced in 62 per cent.

Spinal fluid cell counts returned to normal in 70 per cent., reduced in 25 per cent.

Globulin content counts reduced to normal in 32 per cent., reduced in 24 per cent.

Colloidal gold curve became normal in 35 per cent., reduced in 42 per cent.

As with so many of the pentavalent arsenicals there is a very definite tonic effect, and in general paralysis where epileptiform seizures occur before or after malaria treatment a short course of tryparsamide will prevent their recurrence. As compared with malaria therapy, the results in early cases of neurosyphilis are about the same according to Henderson (1928) and Fong (1928). The advantages of tryparsamide treatment are that it can be given without keeping the patient in hospital and is suitable for old and debilitated persons and those with cardiac and aortic involvement. It is also of service in the treatment of neurosyphilitics in highly malarial countries where many of the patients are already suffering from benign tertian infections. Rayburn and Boyd (1931) believe that changing from tryparsamide to fever treatment or *vice versa* is often of considerable value. Toxic reactions with tryparsamide are not common. There is rarely any Herxheimer reaction and nitroid crises are infrequent. More commonly there are attacks of malaise and slight fever during the first twenty-four hours after an injection. Herpes zoster and, in cases of tabes dorsalis, a widespread and rather irritable, urticaria, have been described. The main danger of the use of tryparsamide is, however, the onset of optic atrophy, which may appear after from 10 to 15 injections. A peripheral constriction of the visual fields to white objects is generally considered a contra-indication to further treatment, at least temporarily.

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Since all early syphilitics are potentially neuro-syphilitics it might be advisable to give a course of tryparsamide as part of the routine treatment of all primary and secondary cases.

Preparation 115.—A compound closely resembling tryparsamide has recently been prepared by Stratman-Thomas, of Wisconsin. It is *n*-phenylglycinemethyl amido-*p* arsinic acid. The drug, which is readily soluble in water, is given intravenously in a 20 per cent. solution, and the dose for an adult is from 2 to 3 gm., though as much as 4 gm. has been given without any ill results. The effects of the compound in the nervous stage of sleeping sickness are very similar to those of tryparsamide, according to van den Branden (1930). In one patient visual disturbances appeared after the administration of 16 gm., though the sight subsequently returned to normal.

This preparation has not yet been tested in neuro-syphilis, though from the resemblance of its constitution, it might be expected to have a very similar action to that of tryparsamide.

Stovarsol, 3-acetylamino-4 hydroxyphenylarsinic acid (acetarsone, spirocid, kharophen, orarsan) is a pentavalent arsenical compound which was first studied by Ehrlich and Hata (1911), and reinvestigated by Fournau and his colleagues (1921 and 1923).

It is a white powder, almost insoluble in water, with an arsenic content of 27.2 per cent., and is of some value in the treatment of amoebiasis, malaria and yaws. Before being employed in these diseases, however, Levaditi and

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Navarro-Martin (1922)¹ had found that it has a curative action in rabbit syphilis, when injected subcutaneously in doses of from 0.1 to 0.2 gm. per kilogram. of body weight. Oral administration was also found to be effective in curing syphilis in both the rabbit and the monkey. Levaditi and Navarro-Martin (1922)² then treated 80 cases of human syphilis with 1 gm. of stovarsol given by mouth for seven days, followed at an interval of a week by a further course until some 12 to 16 gm. had been administered. In 30 cases of primary syphilis the chancre healed in from five to fifteen days, while secondary and tertiary lesions of the skin and mucous membrane also rapidly disappeared. Relapses, however, occurred in many cases. The value of stovarsol as a prophylactic and curative agent in rabbit syphilis was confirmed by Poole (1926), and since then, owing to the fact that it can be given orally with great ease it has been much used in the treatment of congenital syphilis, more especially in Central Europe. Oppenheim (1924), who was perhaps somewhat optimistic in his claims for stovarsol, gave small doses of from 0.1 to 0.2 gm. daily for from three to five days, followed by a rest for a similar period. Soldin and Lesser (1925 and 1928) began with 0.125 gm., daily increasing to 0.5 gm. Spirochætes disappeared rapidly from the primary lesions but to prevent relapse it was necessary to continue treatment for as long as three years, while a total of from 40 to 90 gm. of stovarsol was essential to ensure a cure in congenital syphilis. Müller (1931), who has recently reviewed the stovarsol treatment of congenital syphilis gives a three months' course, seven periods of ten days' treatment alternating with periods of four days' rest. For the first seven days 0.25 gm. is given daily except in the case of very debilitated children, who receive half that amount. During each succeeding treatment-period the daily dose is increased, at first by 0.125 gm., then by 0.25 to 1 gm., so that at the end of the three months 40 to 90 gm. have been given.

Though Cregor and Gastineau (1927) and others believe that stovarsol is more easily tolerated than the arsphenamines, toxic sequelæ are by no means rare. Headache and Herxheimer reactions are not uncommon, while Bender (1927) has reported fever, œdema and jaundice. Porot (1931) has described sensory disturbances and one

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case of pseudo-tabes ; Michael (1929), one of exfoliative dermatitis. Fatal cases have also occurred. One seen by Cazenneuve (1929) was characterised by a bullous skin eruption, diarrhoea and jaundice ; two others recorded by Opitz (1931) were found to have perivascular round celled infiltration in the region of the basal ganglia of the brain, in one accompanied by multiple hæmorrhages.

Incidentally, it may be mentioned that Schamberg (1931) has recently produced a calcium thiosulphate for arsenical dermatitis. This compound, it is claimed, is more efficient than the commonly used sodium thiosulphate.

Apart from the occurrence of toxic reactions, stovarsol, provided that its use is persisted in for some considerable period, does appear to be of definite value in the treatment of congenital syphilis, a value enhanced by its distinct tonic effect and by the ease of its administration.

In other forms of syphilis, stovarsol has not been largely employed. Sézary and Barbé (1929), however, have used it in the treatment of general paralysis of the insane. Among 125 unselected cases the best results were obtained in those suffering from megalomania and other psychical disturbances. Of 31 cases in this category, 17 were able to resume work and 4 others were benefited. The serological reactions were improved in 34 per cent. of all cases, though this improvement bore no relation to the clinical condition. Treatment consisted of three series of injections separated by a month's interval. Injections were given three times a week till each patient had received approximately 20 gm. of the drug.

Calcium stovarsol phosphate, a compound of calcium acetylaminohydroxy-phenylarsinate with calcium glucophosphate was prepared in 1926 by Sabatay of the Pasteur Institute. Though Levy (1929) claims to have obtained some favourable results in syphilis, the principal value of the compound appears to be in its use as a general tonic.

Certain other pentavalent arsenicals which have both trypanocidal and spirochæticidal action require notice. These are acetylarsan, tréparsol, halarsol and Preparation 4002.

Acetylarsan, diethylamine *p* hydroxy-*m*-acetylaminophenyl arsinat, has been used mainly in France in the

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treatment of early syphilis, the chief advantage of the compound being the fact that it can be injected subcutaneously as well as intramuscularly.

In this country Lloyd (1928) has obtained rapid healing of the lesions in 17 primary and 9 secondary syphilitics, spirochætes disappearing from the primary lesions in from six to twenty-four hours after an injection. The total amount of the drug given to adult males was 11 gm., to women 8 to 9 gm., in doses of from 1 to 5 c. The serological reactions were for the most part improved, and in no case of primary syphilis with a negative Wassermann reaction before treatment did a positive reaction develop. Toxic reactions, for the most part trivial, were met with in 14 out of 88 cases. Headache, malaise and a rise in temperature a few hours after injection were the commonest, though vomiting, a slight Herxheimer reaction, transient albuminuria and jaundice occurred in a few cases and in two others there was a toxic erythema.

Tréparsol, *m*-formylamino-*p*-hydroxyphenylarsinic acid contains 28·75 per cent. of arsenic, and resembles stovarsol in that it can be given by mouth. Simon (1924) states that its action in producing a negative Wassermann reaction in primary and secondary syphilis is almost as rapid as that of neoarsphenamine. Although there have been numerous reports of the use of this compound on the Continent, no record of its use in this country has been published. Despite the infrequency of toxic reactions one fatal case has been recorded by Meyer (1929).

Halarsol was originally prepared by Ewins and Everett (1927) and is a 2·5 per cent. stabilised solution of 3-amino-4 hydroxy-phenyl-dichlorarsine.

Experiments on rabbits infected with syphilis showed that the drug caused the disappearance of spirochætes and brought about rapid healing of the lesions. When given by subcutaneous or intramuscular injection, halarsol proved extremely painful. Some success, however, has recently been claimed for the drug by

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Chesterman and Todd (1929) in the treatment of yaws, when the compound is given intravenously. The most recent results obtained (Todd, 1931) show, however, that out of 96 cases of yaws in various stages, 26 relapsed. Levaditi (1931) has also recently reinvestigated its action in syphilis in man, giving weekly intravenous injections of 1 c.c., equivalent to 0.0064 gm. of arsenic. Although primary and secondary lesions healed rapidly the serological reactions still remained positive.

Preparation 4002 is described as a new benzol arsenic acid derivative, though its composition has not been disclosed. It has recently been studied experimentally by Giemsa (1930), and has been found to have a curative action, both in experimental trypanosomiasis and in rabbit syphilis. In the former condition its activity is said to be greater than that of both atoxyl and tryparsamide. In rabbits infected with syphilis, subcutaneous injection of 250 mg. per kilogram of body weight brought about disappearance of the spirochaetes within twenty-four hours and rapid healing of the lesions.

Its chemotherapeutic index is from 1 : 1.6 to 1 : 2. Its curative action is also seen when it is given by mouth. A point of some interest is that from a quarter to a third of the amount of the drug injected remains in the blood serum for at least twenty-four hours. With this greater diffusibility, a property in which the pentavalent arsenicals are superior to the arsphenamine compounds, there seems some hope that the amount of the drug which reaches the spinal fluid after a moderate dose may reach a concentration sufficient to sterilise the tissues.

So far, therefore, no pentavalent arsenic compound has been found to equal in value the trivalent arsphenamines, nevertheless with their greater arsenic content, their tonic action and their greater diffusibility pentavalent arsenicals have inherent qualities which should eventually ensure them a definite place in the chemotherapeutic treatment of syphilis.

Bismuth.—In 1916, Robert and Sauton found that bismuth compounds possessed a curative action in fowl spirochaetosis. Five years later Sazerac and Levaditi showed that syphilis in the rabbit and in man can be cured by bismuth. Since then this aspect of the chemotherapy of syphilis has received perhaps more attention than any other. The absorption and the excretion of

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bismuth, both in man and animals, have been extensively studied and a seemingly inexhaustible supply of new bismuth compounds has been produced, often with little or no preliminary study to determine whether they represent any improvement on those already on the market. It would be as tedious as it would be futile to attempt to deal with all these compounds—there are now more than 200—though it is a moot point whether the time is not rapidly approaching when some international standardisation should be adopted as in the case of the arsphenamines. Such a standardisation would doubtless have been enforced long ago were it not that bismuth salts are possessed of so small a degree of toxicity. At present the variation in actual Bi metal content is from 4 to 98 per cent. Such a variation, however, does not signify much for Giemsa (1922) and Felke (1922), both found that the amount of metallic bismuth necessary to cure rabbit syphilis is extremely small. The chemotherapeutic activity of any compound depends therefore less on its metallic content than on its chemical constitution and physical properties, rate of absorption, rate of excretion and powers of penetration. Absorbability is not, however, everything, for as Greenbaum and Rule (1931) point out, of two compounds with almost equal rates of absorption, one may be spirochæticidal, the other not. Hanzlik and Spaulding (1931) believe that the electrical charge carried by the Bi ion is of considerable importance in connection with permeability, more especially in regard to the power of penetrating into the cerebrospinal fluid, into which anions penetrate more readily than cations. In sodium bismuthate and sodium iodo-bismuthite, for instance, the bismuth ion is negatively charged and penetrates into the cerebrospinal fluid while in bismuth salicylate it is positively charged and does not penetrate. A classification of bismuth compounds on these lines is of considerable interest. The more usual classification of bismuth preparations is into (1) colloidal, (2) water insoluble, (3) water soluble, and (4) fat soluble. While there is now a tendency to neglect insoluble preparations in favour of either water soluble or fat soluble compounds, new preparations of all types continue to appear.

Most interest, however, attaches to the fat soluble preparations which Levaditi (1930) regards as forming a link between the soluble and insoluble products. Although

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first employed by Mulzer, Dahmen, Plaut and others in Germany in 1925 their use did not become general till 1927, when basic α -carboxethyl- β -methyl monoate of bismuth or bivitol and basic methyl hydrocinnamate of bismuth or biazan were introduced. Since that time, according to Schwartz (1930), these two compounds have been employed at the Cochin Hospital in Paris with excellent results, not only to the exclusion of other bismuth compounds but of all other anti-syphilitic remedies. More recently Kolmer (1931) has introduced another fat soluble product, basic bismuth camphocarboxylate (bismo-cymol). This compound contains from 37 to 39 per cent. of bismuth and, in rabbits infected with syphilis, is found to have a chemotherapeutic index of 1 : 15.

A bismuth derivative of an entirely different type has been prepared by Ghosh in India, where it has been used in the treatment of yaws by Chopra, Gupta and Mullick (1928). In the treatment of kala azar various pentavalent antimony compounds have been produced of considerable therapeutic value. One of these compounds is urea stibamine. "Bisnene," in which the bismuth is in pentavalent form, is said to be the analogue of urea-stibamine and is described as the sodium salt of *p*-amino phenyl bismic acid, in combination with urea, the formula being $\text{NH}_2\text{-CO-NH-C}_6\text{H}_4 \cdot \text{BiO(OH)ONO}$. The formula attributed by its author to urea stibamine must, however, be accepted with reserve. Bisnene is said to contain 50.1 per cent. of bismuth and to be suitable for intravenous injection. As much as 3 gm. has been given to a man without producing any toxic reaction, though in the treatment of yaws from 0.1 to 0.175 gm. only is given at weekly intervals. The effect on the healing of yaws is said to be comparable in its rapidity with that seen after the use of arsphenamine compounds.

The possibility of using bismuth analogues of neostibosan and other pentavalent antimony compounds is one deserving of further investigation.

Bismuth and Arsenic Compounds.—Although the controversy between those who use arsenic and bismuth contemporaneously and those who use them alternately

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is by no means at an end, there have been prepared a number of compounds of bismuth with arsenic, both in the trivalent and pentavalent form. These compounds are :—

- (i.) Bismuth arsphenamine sulphonate (bismarsen).
- (ii.) Bismuth stovarsol (bistovol).
- (iii.) Bismuth tryparsamide.
- (iv.) Bismuth arsanilate.
- (v.) Bismuth cacodylate.
- (vi.) Bismuth arseno-pyridine.

Bismarsen.—Bismuth arsphenamine sulphonate was first prepared by Raiziss in 1925, and contains from 12 to 15 per cent. of arsenic and from 23 to 25 per cent. of bismuth. It is a yellow powder readily soluble in water and is injected intramuscularly in doses of 0.2 gm., dissolved in 1 c.cm. of distilled water, to which is sometimes added a little butyn as an anæsthetic, as, though there is no pain at the site of injection in ambulatory patients, those who are confined to bed sometimes complain of discomfort. Stokes and Chambers (1927), who were the first to use the drug clinically, gave 2 injections a week for fourteen weeks, four such courses separated by intervals of a fortnight being administered in all. In patients with primary and secondary syphilis the healing effect was slow as compared with the arsphenamines, though the tonic effect was greater and the toxic sequelæ less numerous. These results have been confirmed by Elliott (1929), Templeton (1929), Kolmer (1930), and Stokes, Miller and Beerman (1931). O'Leary and Brunstig (1930) have found that in the treatment of acute syphilis the incidence of relapse, particularly in the central nervous system, is more frequent than with other systems of treatment used in acute syphilis. In neurosyphilis the only form definitely improved according to Shivers (1930) is the acute meningeal type. In tabes there is some amelioration of the lightning pains and a gain in weight, but no change in the ataxia, optic atrophy or spinal Wassermann reaction. Rayburn and Boyd (1930) emphasise the fact that some individuals with neurosyphilis who are intolerant to arsenic in any other form can nevertheless tolerate it in the form of bismarsen.

All who have worked with this compound have been struck by the infrequency of toxic sequelæ. Among

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5,345 injections there were only 5 slight nitroid crises, 2 cases of exfoliative dermatitis and 1 sterile abscess. Schoch (1930) has also reported 1 case of hypersensitive-ness in a patient receiving bismarsen, the arsenobenzol radical being the cause of the reaction. The low toxicity, the tonic effect and the ease of administration are the chief advantages which may be urged in favour of bismarsen.

Bistovol, the basic bismuth salt of *m*-acetylamino-*p*-hydroxyphenyl-arsenic acid was first used by Levaditi (1925) in experiments on rabbit syphilis. It contains 15 per cent. arsenic and 41 per cent. bismuth and is injected as a 10 per cent. solution in oil. Although Levaditi and Fournier (1928) state that it has a chemotherapeutic index of 1 : 35 it has not been extensively tested in human syphilis. The same is true of *Bismuth tryparsamide*, also tested by Levaditi (1928) in experimental syphilis in the rabbit.

Bismuth arsanilate, prepared by Shircore (1926), was employed in the treatment of yaws and syphilis in Tanganyika territory. In rabbit syphilis its curative action was somewhat slower than that of stovarsol.

Bismuth cacodylate, the bismuth salt of dimethyl arsenic acid is a French preparation containing 27 per cent. of arsenic and 29.4 per cent. of bismuth. It is

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soluble in water and can be injected intramuscularly without causing pain or sterile abscesses. Montlaur and Picon (1930) find, however, that though the salt is somewhat unstable it can be given to patients who are intolerant to other forms of arsenic and bismuth. A high urea content of the blood is not a contra-indication, as this preparation does not tend to increase the urea as do other salts of bismuth.

Bismuth Arseno-pyridine.—Psiothanol was originally used by Jausion, Debucquet and Pecker (1929) in the treatment of psoriasis and has now been employed as an anti-syphilitic by Jausion and Pecker (1930). It is a mixture of an arseno-pyridine compound combined with bismuth hydroxy-dicarboxyl-diethyl-diamino-isobutyrate. It is soluble in water and is put up in ampoules of 3.5 cm., each of which corresponds to 0.06 gm. of the bismuth salt and 0.05 gm. of the arsenic compound or 25 mg. of Bi and 12 mg. of As. Injections may be given intramuscularly or intravenously, the latter for preference, at intervals of 2 days. The injections at first are 1.5 cm., then 3.5 cm., 20 injections constituting a course which is repeated after an interval of a month. The injections are almost painless, except that a few minutes after the injection there is often an aching in the jaws which is of short duration. Headache and sickness are rare, though diarrhoea an hour after the injection is very common. Jausion and Pecker (1930) state that in 3 cases of primary syphilis with negative Wassermann reactions, healing of the lesions occurred after from 3 to 7 injections; in early cases with primary and secondary lesions the Wassermann reaction become negative after one course of injections while only 1 case required 40 injections; in 9 secondary cases, already treated without result by arsphenamine and fat soluble bismuth solutions, the Wassermann reaction was made negative by 40 injections.

A point of some interest in regard to these bismuth arsenic compounds is that there is no record of any undue tendency to the development of drug resistant spirochætes.

Tellurium was first tested for spirochæticidal properties by Levaditi and Nicolau (1926), who found that it had both a curative and a powerful prophylactic action in experimental rabbit syphilis and in rabbits infected with

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S. cuniculi. Metallic tellurium suspended in glucose, tellurium oxide and tellurium iodoquinine in oil were the most effective preparations and were less toxic than the soluble preparations. These same insoluble tellurium preparations were also used by Fournier and Levaditi (1926 and 1927), and Levaditi, Nicolau and Manin (1927) in the treatment of human syphilis, with improvement in the Wassermann reaction and healing of the lesions. Of 14 cases treated with tellurium alone, 12 improved, 1 relapsed and 1 was entirely resistant. In 2 cases of neuro-syphilis there was subjective improvement and a general tonic effect. Although in early syphilis the results are less rapid than with arsenic or bismuth, toxic reactions were few except when large doses were given or the number of injections was greatly increased. A slight bluish discolouration of the skin, especially where it is exposed to sunlight, has been described by Bory (1927), while Vesari (1928) found that his patients decreased in weight. Loss of pigment from the hair also occasionally occurs. The great drawback to the use of tellurium is the fact that the element is eliminated not only by the kidneys and intestine but also by the lungs as a methyl telluride, with the result that the patient lives and moves in an odour of garlic for weeks and even months. In this country Frazer (1930) has studied the effect of tellurium metal on cases with resistant Wasserman reactions of an average duration of nineteen years. Injection of from 0.5 to 1 c.c. of a 5 per cent. suspension were given at intervals of from five to seven days to a total of 5 c. cm. In 4 out of 7 cases the Wassermann reaction was favourably influenced.

Vanadium was first used as tetra- and hexa-vanadate of sodium and potassium by Proescher, Seil and Stillians (1917), who found that both in the rabbit and in man there occurred a rapid disappearance of spirochætes, healing of the lesions and a more or less definite improvement in the serological reactions. These results were confirmed by Fournier, Levaditi and Schwartz (1922), who cured rabbits infected with syphilis by subcutaneous injections of from 15 to 20 mg. per kilogram of sodium potassium tartro-vanadate.

Platinum does not appear to have been used in the treatment of syphilis in man but as the double hyposulphite of sodium and platinum it was found by Levaditi,

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Girard and Nicolau (1923) to have some curative action in rabbit syphilis.

Antimony, despite its action in trypanosomiasis, has only a very feeble action on infections due to *S. pallida*. A recent preparation by Lumière, stibiothio-propanol sulphonate of sodium has been shown by Lépine (1931) to compare favourably with other antimonials in the treatment of experimental trypanosomiasis in rabbits and mice, but to be active only in maximum doses on infections due to *S. pallida* and *S. cuniculi*, while relapses soon occur.

Thorium was found by Klauder (1924) to possess some slight curative action in experimental syphilis in the rabbit, though Levaditi and Lépine (1931) have been unable to confirm these results.

Stronmium has also recently received some attention from Italian workers. Ciambellotti (1930), using an organic stronmium preparation known as 418 Sr., has found that in the treatment of human syphilis it has little curative action in the acute stage, though in old syphilitics it reduces the Wassermann reaction and in tabes dorsalis it relieves the lightening pains.

Indium and Gallium.—In the course of their survey of the elements for spirochæticidal properties, Levaditi and Lépine (1931) have found that indium possesses these properties to a slight degree. The rare metal gallium was also found by Levaditi, Bardet, Tchakirian and Vaisman (1931) to have a curative action in experimental syphilis of the rabbit. The soluble tartrate was more active than the insoluble preparations, the oxide being without any definite action.

Gold.—According to Lebeuf and Mollard (1931), Chrostien of Montpellier more than a century ago employed gold chloride and the double chloride of sodium and gold as anti-syphilitics. Neisser (1911), who was the first to test the spirochæticidal action of colloidal gold in syphilitic monkeys could, however, discover no curative action, though shortly afterwards Truffi (1913) found that gold chloride had an effect on syphilis in the rabbit. These results were confirmed by Kolle and Ritz (1919), Doulcet (1922) and Klauder (1924). In 1925, Levaditi, Girard and Nicolau found that the double hyposulphite of sodium and gold, sanocrysin— $(\text{AuS}_2\text{O}_3\text{Na}) \text{Na}_2\text{S}_2\text{O}_3$ had a curative action in rabbits suffering from infections

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due to *S. pallida* and *S. cuniculi*, though the effects were less marked than with bismuth. In the same year Feldt (1925) also published his observations on the action of gold in relapsing fever of mice and rats, and in rabbit syphilis; the compounds studied included colloidal gold, the double cyanide of gold and potassium, the double chloride of sodium and gold, sanocrysin, krysolgan (the sodium salt of *p*-amino-*o*-auromercaptobenzenecarboxylic acid), solganal (the di-sodium salt of *p*-sulphomethyl-amino-*o*-auromercaptobenzene sulphonic acid), solganal B and various commercial preparations of gold, of undisclosed composition, such as triphal, lopion and allochrysin. Most interest attaches to solganal B, aurothio-glucose, which can be injected subcutaneously or intramuscularly. Its chemotherapeutic index in rabbits infected with syphilis is according to Feldt (1930) 1:75, as compared with solganal 1:30, sanocrysin 1:2.5 and neosalvarsan 1:10. Its toxicity for laboratory animals is one-fiftieth that of the double cyanide of gold and potassium, one-tenth that of sanocrysin. In rabbits infected with scrotal chancres there is complete healing twenty-three days after an injection of 0.025 gm. per kilogram of body weight, while spirochætes disappear from the lesions after four days. If an injection of 0.04 gm. per kilogram be given, spirochætes disappear in two days, while with 0.5 gm. they disappear in one day. A point of some interest is that in normal dogs injected with solganal B there is an accumulation of gold in the brain.

As a result of the experimental researches of Levaditi and his colleagues, Fournier and Mollaret (1925) investigated the action of sanocrysin on syphilis in man. When given intravenously in doses of 1 gm. at short intervals there was a rapid disappearance of the spirochætes, healing of the lesions and an improvement in the serological reactions. With smaller doses of from 0.25 to 0.5 gm., the action was slower and in some cases no improvement occurred. Toxic reactions, skin eruptions and albuminuria were frequent.

In 1926 the same workers reported their results with a hyposulphite of sodium and gold suspended in oil and given intramuscularly in doses up to 1 gm. The clinical and serological results were much superior to those obtained with the intravenous injections, possibly owing

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to the slow absorption and more prolonged action. The intramuscular route has also been used by Luttenberger (1931) in experiments with solganal B. Sixty-five cases of primary and secondary syphilis with positive Wassermann reactions were treated, a first injection of 0.25 gm. being followed 3 days later by 0.5 gm., this dose being continued until a total of 5 to 6 gm. had been administered. Spirochætes disappeared from the lesions after from 1 to 1.5 gm. had been injected, while the Wassermann reactions themselves became negative in all cases, though in some the Meinicke reaction remained positive. In 1 case of neuro-syphilis with a positive spinal Wassermann, and a positive colloidal gold test, the administration of 4.75 gm. of solganal B in 7 weeks caused both reactions to become negative. One case has been successfully treated with solganal B, 1 case where the Wassermann reaction had remained positive for many years.

Recently Lebeuf and Mollard (1931) have treated 15 cases of early syphilis with gold salts; 13 were treated with intravenous injections of the double hyposulphite of sodium and gold. Doses of from 0.05 to 0.25 gm. were insufficient to produce any result, but from 0.25 to 0.5 gm. given every 3 days to a total of 5 gm. caused rapid disappearance of spirochætes and healing of the lesions. Serological reactions were uninfluenced. Two cases were treated by intramuscular injections of solganal B, the first receiving a total of 5.25 gm., the other 7 gm. In both cases, after 2 injections, spirochætes had disappeared from the lesions which healed with rapidity. In 1 case the Wasserman reaction became negative, in the other it was reduced.

There are two objections to the employment of gold in the therapy of syphilis, the high price and the frequency of toxic reactions. With solganal B reactions are intense, and skin eruptions, amounting even to exfoliative dermatitis are not uncommon. There is also severe pain at the site of injection. Heuck and von Kennel (1931), however, have found that toxic reactions to gold can be markedly reduced if, during the period of treatment and for at least a week afterwards, the patients eat from 50 to 100 gm. of glucose a day.

Further observations on the gold therapy of syphilis are highly desirable. It is open to question, however,

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whether gold has any direct spirochæticidal action and whether its therapeutic value in syphilis, as in tuberculosis, is not due to the production of a form of protein shock.

Mercury.—It is perhaps not surprising that comparatively few fresh preparations of mercury have recently been prepared. Hille (1927) has produced a colloidal mercury sulphide which can be given intramuscularly in doses of 4 c.cm. without causing local pain or risk of nephritis. According to Wakerlin (1929) this preparation is of value in old syphilitics whose Wassermann reaction is still positive after prolonged treatment with arsenic and bismuth. It is not improbable that certain of the good results of injecting this colloid are due to the protein shock, induced by the protein-like materials used as colloid protectors.

Sulphur.—Recently beneficial results have been obtained both in neuro-syphilis and in early syphilis by the injection of sulphur, either in colloidal form or as a suspension. Schroeder (1929) employs a 1 per cent. suspension of sublimated sulphur in olive oil. The first injection is from 0.5 to 1 c.c.; later injections are increased by 1 c. cm. In neuro-syphilis, in recent secondary syphilis and in congenital syphilis it is claimed that remarkable improvement has occurred. Bory (1930) believes that the injection of sulphur in association with bismuth improves the therapeutic action. It seems probable that the rise in temperature caused by the sulphur is of assistance in stimulating the defence mechanism of the body, as Dennie, Gilkey and Pakula (1931) have recently shown that malaria therapy is of considerable value in early cases of acute interstitial keratitis and in hyperplastic bone syphilis, a result which they believe is due to the stimulating effect of the malaria parasite on the phagocytes of the body.

THE ERADICATION OF SYPHILITIC INFECTION FROM THE BODY

This brief survey of recent advances in the chemotherapy of syphilis shows that it is by no means difficult to heal the primary and secondary lesions of syphilis by the administration of a variety of drugs. From the public health point of view this is a matter of the greatest

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importance since the syphilitic patient is no longer an active focus of infection. By appropriate means also it is not impossible to change even a resistant Wassermann reaction from positive to negative. But the question remains, does the rapid healing of primary and secondary lesions under the influence of modern anti-syphilitics necessarily imply the destruction of spirochætes in the central nervous system and great blood vessels? Does the conversion of a resistant positive Wassermann reaction into a negative one imply anything more than a slight increase in the antibody titre of the serum, such an increase for instance as is brought about by the injection of manganese into a horse immunised against diphtheria toxin? Warthin (1929), it will be remembered, stated that he had never seen at necropsy a case of perfectly healed syphilis, as search, often prolonged it is true, invariably revealed active latent lesions in the aorta, heart or other organ. The only unequivocal evidence of cure to be obtained during life in man is definite evidence of reinfection. Stokes, Schoch and Ireland (1931) have recently analysed the history of 2,439 cases treated by modern anti-syphilitics, 4 only were possible cases of reinfection, and in none of these was the evidence of reinfection indisputable. French observers, with greater optimism but less critical acumen, have encountered numerous cases of reinfection. It is obvious that much that has passed for complete cure is in reality asymptomatic latency. Little value can, unfortunately, be attached to the removal of superficial lymph glands from human syphilitics and their intratesticular inoculation in rabbits. With or without treatment the superficial lymph glands tend to become sterile.

Certain experiments of Schlossberger (1929) are, however, of interest in this connection. When syphilitic spirochætes are injected subcutaneously in mice they pass not only to the lymph glands and spleen, but fourteen days after inoculation they reach the central nervous system. If neo-arsphenamine or solganal B are given during those fourteen days, spirochætes never reach the brain, for they are killed; but there are only fourteen days of grace, and after they have once reached the central nervous system they cannot be eradicated.

The question whether syphilis can really be eradicated can only be determined by the careful correlation, in a

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large series of cases, of the pathological changes found at necropsy with the treatment given during life. To obtain such a large series of cases it may be necessary to wait for that medical Utopia in which each person shall carry with him his medical history sheet. In the meantime much might be done in our large hospitals by a closer co-operation between the pathologist and the venereal specialist.

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